JOC*Article*

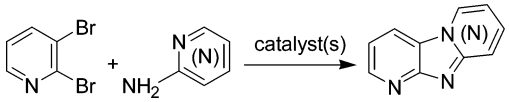
Orthogonal and Auto-Tandem Catalysis: Synthesis of Dipyrido[1,2-*a*:2′,3′-*d*]imidazole and Its Benzo and Aza Analogues via Inter- and Intramolecular C−N Bond Formation

Kristof T. J. Loones, Bert U. W. Maes,* Caroline Meyers, and Joke Deruytter

Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium

bert.maes@ua.ac.be

Received October 5, 2005



The synthesis of dipyrido[1,2-*a*:2′,3′-*d*]imidazole and hitherto unknown benzo and aza analogues is described. These relatively complex polycyclic heterocycles could be smoothly prepared in one step from commercially available building blocks. Mechanistically, the developed procedure involves orthogonal (Pd and Cu catalyst) or auto-tandem (Pd catalyst) catalysis via regioselective inter- and intramolecular C−N bond formation.

Introduction

Tin-free palladium-catalyzed amination, pioneered by the teams of Buchwald and Hartwig, has established itself as the most powerful tool hitherto available for the construction of C(sp^2)−N bonds.[1,2] Since the mid nineties, the substrate scope of the method has been seriously expanded, mainly by the development of new ligands for the transition metal.[2] Meanwhile, the Buchwald−Hartwig reaction has also been successfully adopted in heterocyclic chemistry for the decoration and construction of nitrogen-containing heterocyclic skeletons.[2−4] Within the latter research field, the most recent challenge is to search for tandem-catalyzed processes.[5−7] These provide a serious advantage because relatively complex entities can be built up in a one-pot process starting from readily available building blocks and may prove to be highly valuable in library development in pharmaceutical and agrochemical discovery programs. Hitherto, only a few tandem double-palladium-catalyzed amination reactions have been reported in the literature.[6,7] Three reports deal with the construction of the pyrrole entity in carbazoles and dithieno[3,2-*b*:2′,3′-*d*]pyrroles via double N-arylation of primary amines with 2,2′-di(pseudo)-halobiaryls.[6a−c] Willis used a similar approach starting from 2-(2-halophenyl)ethen-1-yl triflates and primary amines to build up the pyrrole unit of indoles.[6d] Our research group described the construction of the imidazole entity in dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo and aza analogues via a double N-arylation of amino(di)azines with 2-chloro-3-iodopyridine.[7]

(1) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1348. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

(2) For recent reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

(3) For examples of the decoration and construction of nitrogen-containing heterocycles via palladium-catalyzed C−C and C−N bond-forming reactions, see: (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000. (b) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625.

(4) For examples of the synthesis of nitrogen-containing heterocycles via the use of an intramolecular Pd-catalyzed amination, see the following references. (a) For indoles, see: Brown, J. A. *Tetrahedron Lett.* **2000**, *41*, 1623. (b) For indolines, 1,2,3,4-tetrahydroquinoline and 2,3,4,5-tetrahydro-1*H*-1-benzazepine, see: Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (c) For α-carboline, see: Abouabdellah, A.; Dodd, R. H. *Tetrahedron Lett.* **1998**, *39*, 2119. (d) For indazoles, see: Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519. (e) For phenazines, see: Emoto, T.; Kubosaki, N.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **2000**, *41*, 355. (f) For benzimidazoles, see: Brian, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893. (g) For pyrido[1,2-*a*]benzimidazole, see: Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505. (h) For oxazepine and thiazepine, see: Margolis, B. J.; Swidorski, J. J.; Rogers, B. N. *J. Org. Chem.* **2003**, *68*, 644.

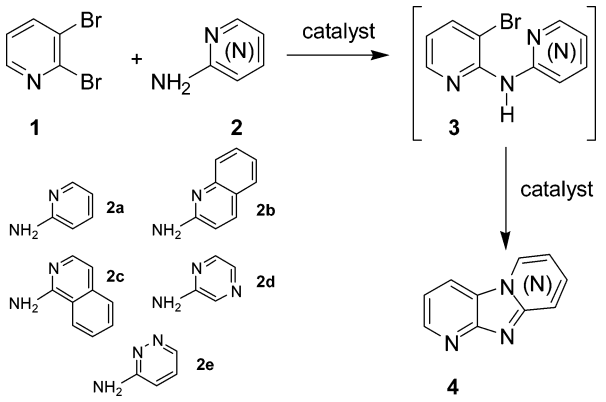
(5) For examples of tandem-catalyzed reactions that involve palladium-catalyzed C−N and C−C bond formation, see: (a) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Org. Chem.* **2003**, *68*, 6011. (b) Dajka-Halász, B.; Monsieurs, K.; Éliás, O.; Károlyházy, L.; Tapolcsányi, P.; Maes, B. U. W.; Riedl, Z.; Hajós, G.; Dommisse, R.; Lemière, G. L. F.; Košmrlj, J.; Mátyus, P. *Tetrahedron* **2004**, *60*, 2283. (c) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906.

(6) Carbazoles and dithieno[3,2-*b*:2′,3′-*d*]pyrroles: (a) Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H.-Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2051. (b) Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2005**, *70*, 413. (c) Koeckelberghs, G.; De Cremer, L.; Vanormelingen, W.; Dehaen, W.; Verbiest, T.; Persoons, A.; Samyn, C. *Tetrahedron* **2005**, *61*, 687. Indoles: (d) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403.

(7) Dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo and aza analogues: Loones, K. T. J.; Maes, B. U. W.; Dommisse, R. A.; Lemière, G. L. F. *Chem. Commun.* **2004**, 2466.

10.1021/jo052091u CCC: $33.50
Published on Web 11/22/2005

SCHEME 1. Synthesis of Dipyrido[1,2-*a*:2′,3′-*d*]imidazole and Its Benzo and Aza Analogues via Tandem Catalysis



This is the first report on tandem-catalyzed aminations in which regioselectivity issues, via chemoselective oxidative addition, are incorporated. These few published examples are all of the auto-tandem catalysis type.[8] In this article, we report the synthesis of dipyrido[1,2-*a*:2′,3′-*d*]imidazole and its benzo and aza analogues via auto-tandem or orthogonal tandem inter- and intramolecular amination. Double amination via orthogonal tandem catalysis is unprecedented in the literature.

Results and Discussion

In continuation of our recent work on the synthesis of dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo and aza analogues via auto-tandem Pd-catalyzed double amination of 2-chloro-3-iodopyridine with amino(di)azines, we became interested in the use of 2,3-dibromopyridine (**1**) as an amination substrate (Scheme 1).[7,9] In this way, regioisomeric dipyrido[1,2-*a*:2′,3′-*d*]imidazole and its benzo and aza analogues should be accessible. We chose the coupling of **1** with 2-aminopyridine (**2a**) as a test case. Unfortunately, neither of the reaction conditions previously developed for 2-chloro-3-iodopyridine worked because only *N*-(3-bromopyridin-2-yl)pyridin-2-amine[10] (**3a**) could be obtained and no dipyrido[1,2-*a*:2′,3′-*d*]imidazole (**4a**).[7,9,11a] To identify Pd catalysts potentially suitable for auto-tandem catalysis, we first looked in more detail at the Pd-catalyzed intramolecular amination of **3a**. Several phosphine ligands (P(*t*-Bu)$_3$,[12] DTPB (JohnPhos),[13] DCPB,[13] DCPAB (DavePhos),[13] and DPEphos[14]) were tested in refluxing toluene or dioxane using a mild Cs_2CO_3 base.[11b] However, none of these trials gave **4a**. Also, with the carbene ligand IPr,[15] no trace of the cyclized product **4a** could be found.[11b] As a consequence of these failures, we turned our attention toward copper catalysis.[16] Interestingly, the use of nitrogen-based bidentate ligands in combination with a weak Cs_2CO_3 base in DME gave conversion to **4a**. A solution of 5 mol % CuI/10 mol % 1,10-phenanthroline[17] yielded 72% **4a** and 24% recovery of **3a** in a reaction time of 17 h (Table 1, entry 1). In the same reaction time, 5 mol % CuI/10 mol % *rac-trans*-1,2-cyclohexanediamine[18] as well as the use of 5 mol % CuI/10 mol % *N*,*N*′-dimethyl-1,2-ethanediamine[18] gave 70% **4a** and 18% recovered starting material **3a** (Table 1, entries 3 and 4). Increasing the catalyst loading of the CuI/phenanthroline system to 7.5 mol % allowed the complete conversion of **3a**, and **4a** could be isolated in 95% yield (Table 1, entry 2). For the copper catalysts based on *rac-trans*-1,2-cyclohexanediamine and *N*,*N*′-dimethyl-1,2-ethanediamine starting material, **3a** still remained using 7.5 mol %.

TABLE 1. Cu-Catalyzed Intramolecular Amination of 3a[a]

entry	ligand[b] Cu(I)	loading Cu(I) (mol %)	Cu/L	time (h)	**3a** (%) recovery	**4a** (%)
1	A	5	1/2	17	24	72
2	A	7.5	1/2	17	0	95
3	B	5	1/2	17	18	70
4	C	5	1/2	17	18	70

[a] CuI, ligand, **3a** (0.5 mmol), Cs_2CO_3 (1.0 mmol), and DME (4 mL) at 95 °C (oil bath). Experiments were performed in a 10 mL microwave vial. [b] A: 1,10-phenanthroline. B: *rac-trans*-1,2-cyclohexanediamine. C: *N*,*N*′-dimethyl-1,2-ethanediamine.

At this stage of the research program, we wondered if it would be possible to prepare **4a** directly from **1** and **2a** via orthogonal tandem catalysis (simultaneously operating palladium and copper catalysts). Gratifyingly, we found that the use of 2 mol % $Pd_2(dba)_3$/4.4 mol % 9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene (XANTPHOS) and 10 mol % CuI/20 mol % 1,10-phenanthroline with Cs_2CO_3 as the base in refluxing DME gave 55% of **4a** and only traces of the intermediate **3a** (<2%) in a 24 h reflux (Table 2, entry 1). However, 41% of **1** was also recovered. When we executed the same reaction in a one-pot two-step process, 42% of **4a** and 53% of **3a** were isolated (Table 2, entry 2). This one-pot two-step process involves Pd-catalyzed intermolecular amination for 7 h followed by the addition of a copper catalyst and a subsequent 17 h reflux.[19] Interestingly, following this protocol, no **1** was recovered. Comparison of this experiment with the orthogonal tandem catalysis clearly indicates that in the latter case the copper catalyst has an inhibition effect on the Pd-catalyzed intermolecular amination reaction. When the 1,10-phenanthroline ligand was omitted, orthogonal tandem Pd and Cu catalysis gave 34% **4a**, 7% **3a**, and 49% unconverted **1** (Table 2, entry 3). Because of the structural similarity between 1,10-phenan-

(8) For taxonomy of tandem catalysis, see: Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365.

(9) (a) Maes, B. U. W.; Loones, K. T. J.; Jonckers, T. H. M.; Lemière, G. L. F.; Dommisse, R. A.; Haemers, A. *Synlett* **2002**, 1995. (b) Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemière, G. L. F.; Dommisse, R. A. *J. Org. Chem.* **2004**, *69*, 6010.

(10) The C-2 chemoselective amination on **1** was confirmed via a C−Br hydrogenolysis reaction on the obtained *N*-(3-bromopyridin-2-yl)azaheteroarylamines.

(11) For details, see Supporting Information. (a) Table A. (b) Table B. (c) Temperature measured inside the vessel (fiber optic probe). Oil bath temperature = 160 °C. (d) For attempts to perform auto-tandem Cu-catalyzed double amination, see Table C.

(12) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

(13) DTPB = 2-(di-*tert*-butylphosphanyl)biphenyl (JohnPhos), DCPB = 2-(dicyclohexylphosphanyl)biphenyl, DCPAB (DavePhos) = 2-dicyclohexylphosphanyl-2′-(*N*,*N*-dimethylamino)biphenyl. Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

(14) DPEphos = bis[2-(diphenylphosphanyl)phenyl] ether. (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694. (b) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327.

(15) IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69.

(16) For recent reviews, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.

(17) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133.

(18) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684.

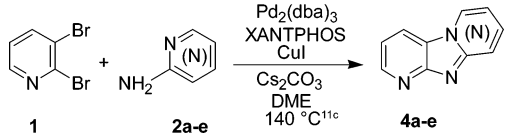
(19) The intermolecular Pd-catalyzed amination of **1** with **2a** was finished after 7 h, as judged by TLC and MS analysis.

TABLE 2. Orthogonal Tandem Pd- and Cu-Catalyzed Amination of 1 with 2-Aminopyridine (2a)[a,11]

entry	ligand[b] Pd(0) Cu(I)	loading Pd(0)/Cu(I) (mol %)	Pd/L Cu/L	time (h)	**1**(%) recovery	**3a**[10] (%)	**4a**[23] (%)
1	D	4	1/1.1	24	41	traces	55
	A	10	1/2				
2	D	4	1/1.1	7/17	0	53	42
	A	10	1/2				
3	D	4	1/1.1	24	49	7	34
		10					
4	D	4	1/1.1	24	0	0	80[c]
		10					
5	D	4	1/1.1	7/17	0	0	88[c]
		10					

[a] $Pd_2(dba)_3$, XANTPHOS, CuI, ligand, **1** (1.5 mmol), **2a** (1.8 mmol), Cs_2CO_3 (6.0 mmol), and DME (15 mL), at reflux. [b] A: 1,10-phenanthroline. D: XANTPHOS. [c] 140 °C.[11c]

TABLE 3. Orthogonal Tandem Pd- and Cu-Catalyzed Amination of 1 with Amino(di)azines (2)[a,11]



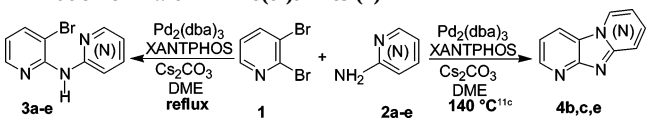
1 **2a-e** **4a-e**

entry	**2**	ligand[b] Pd(0) Cu(I)	loading Pd(0)/Cu(I) (mol %)	Pd/L	time (h)	**1**(%) recovery	**3**[10] (%)	**4**[23] (%)
1	**2a**	D	4	1/1.1	24	0	0	80
			10					
2	**2b**	D	4	1/1.1	24	0	0	88
			10					
3	**2c**	D	4	1/1.1	24	<5	5	77
			10					
4	**2c**	D	4	1/1.1	30	0	0	86
			10					
5	**2d**	D	4	1/1.1	24	0	0	44
			10					
6	**2e**	D	4	1/1.1	24	18	2	63
			10					
7	**2e**	D	8	1/1.1	24	6	6	70
			10					
8	**2e**	D	8	1/1.1	30	0	0	76
			10					

[a] $Pd_2(dba)_3$, XANTPHOS, CuI, **1** (1.5 mmol), **2** (1.8 mmol), Cs_2CO_3 (6.0 mmol), and DME (15 mL), at 140 °C.[11c] [b] D: XANTPHOS.

throline and **4a**, purification via column chromatography on silica gel was very time consuming. Therefore, we decided to continue our optimization experiments on **1** with **2a** with CuI without an added nitrogen bidentate ligand. Interestingly, performing the test-case coupling in a pressure tube at 140 °C[11c] for 24 h gave a complete conversion of **1** to **4a** and an isolated yield of 80% (Table 2, entry 4). The same reaction gave only a slightly higher yield (88%) when a one-pot two-step process was followed (Table 2, entry 5).[19] With our optimized orthogonal tandem inter- and intramolecular amination protocol, several other aminoazines (2-aminoquinoline (**2b**) and 1-aminoisoquinoline (**2c**)) and aminodiazines (aminopyrazine (**2d**) and 3-aminopyridazine (**2e**)) could be smoothly coupled with **1** (Table 3). Mechanistically, we assume that in the Cu-catalyzed intramolecular amination precoordination of the amidine imine nitrogen atom of the azaheteroarylamine moiety of **3** to CuI facilitates oxidative addition.[16] This view is supported by the fact that pyridine itself has been described as a possible ligand

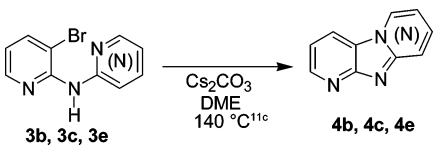
TABLE 4. Auto-Tandem Pd-Catalyzed Inter- and Intramolecular Amination of 1 with Amino(di)azines (2)[a,11]



entry	amidine **2**	ligand[b] Pd(0)	loading Pd(0) (mol %)	Pd/L	time (h)	reaction temp	**1** (%) recovery	**3**[10] (%)	**4**[23] (%)
1	**2a**	D	4	1/1.1	7	reflux	2	91	0
2	**2a**	D	4	1/1.1	24	140 °C	0	79	4
3	**2b**	D	4	1/1.1	7	reflux	0	99	0
4	**2b**	D	4	1/1.1	24	140 °C	0	0	93
5	**2c**	D	4	1/1.1	7	reflux	29	67	0
6	**2c**	D	4	1/1.1	17	reflux	18	75	0
7	**2c**	D	8	1/1.1	7	reflux	0	91	0
8	**2c**	D	4	1/1.1	24	140 °C	0	0	76
9	**2d**	D	4	1/1.1	17	reflux	11	85	0
10	**2d**	D	8	1/1.1	7	reflux	0	92	0
11	**2d**	D	4	1/1.1	24	140 °C	0	69	5
12	**2e**	D	4	1/1.1	7	reflux	0	81	0
13	**2e**	D	4	1/1.1	24	140 °C	0	0	97

[a] $Pd_2(dba)_3$, XANTPHOS, **1** (1.5 mmol), **2** (1.8 mmol), Cs_2CO_3 (6.0 mmol), and DME (15 mL), at reflux or 140 °C.[11c] [b] D: XANTPHOS.

TABLE 5. Attempts to Perform Intramolecular Amination on 3b, 3c, and 3e without the Addition of a Pd or Cu Catalyst[a]



entry	**3**	time (h)	**3**(%) recovery	**4**(%)
1	**3b**	24	39	53
2	**3c**	24	0	92
3	**3e**	24	78	16

[a] **3** (0.5 mmol), Cs_2CO_3 (2.0 mmol), and DME (5 mL), at 160 °C (oil bath). Experiments were performed in an oil bath in a 10 mL microwave vial.

for CuI in amination reactions.[20] Alternatively, the reaction products **4** can also act as ligand.[21]

To exclude the occurrence of an auto-tandem Pd-catalyzed double amination process at 140 °C,[11c] we reexamined all coupling reactions on **1** with 2 mol % $Pd_2(dba)_3$/4.4 mol % XANTPHOS.[11d] Remarkably, at this higher reaction temperature, double amination with 2-aminoisoquinoline (**2b**), 1-aminoquinoline (**2c**), and 3-aminopyridazine (**2e**) took place smoothly (Table 4, entries 4, 8, and 13), whereas exactly the same reactions executed at reflux temperature only gave the respective intermediates **3** (Table 4, entries 3, 7, and 12).

Interestingly, the attempted ring closure of **3b**, **3c**, and **3e**, without adding a Pd catalyst, revealed that in the case of **3c** complete conversion to **4c** occurred and consequently no catalyst is required to perform a ring closure on **3c** (Table 5, entry 2). Therefore, mechanistically, the coupling of **1** with **2c** cannot be labeled as auto-tandem Pd catalysis (although Pd-catalyzed and -uncatalyzed ring closures of **3c** probably do occur simultaneously), whereas the formation of **4b** and **4e** takes place, at least partly, via auto-tandem Pd-catalyzed inter- and intramo-

(20) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143.

(21) Lu, J. Y.; Cabrera, B. R.; Wang, R. J.; Li, J. *Inorg. Chem.* **1998**, *37*, 4480.

lecular amination (Table 5, entries 1 and 3). The remarkable temperature-selective behavior with **2b** and **2e** can be rationalized via a temperature-dependent oxidative addition on the intermediates **3b** and **3e**. To the best of our knowledge, reaction product control in palladium-catalyzed aminations by altering the reaction temperature is hitherto unprecedented. In contrast, amination of **1** with 2-aminopyridine (**2a**) and 2-aminopyrazine (**2d**) at 140 °C almost exclusively gave the corresponding intermediates **3a** and **3d** (Table 4, entries 2 and 11). Only trace amounts of the respective tricyclic compounds **4a** and **4d** were isolated. Consequently, to obtain **4a** and **4d** at 140 °C, an orthogonal tandem Pd- and Cu-catalyzed process is required.

In summary, we have developed a regioselective orthogonal tandem-catalyzed amination based on a chemoselective oxidative addition, in which a Pd-catalyzed intermolecular amination and a Cu-catalyzed intramolecular amination occur consecutively. In addition, a hitherto unprecedented process control (regioselective intermolecular or auto-tandem inter- and intramolecular Pd-catalyzed amination) in Buchwald−Hartwig reactions by a simple alteration of the reaction temperature is also presented. The developed method gives access to unknown polycyclic aza heteroaromatic skeletons with potential antitumor properties in a simple and straightforward way.[22]

Experimental Section

General Procedure for the Synthesis of Dipyrido[1,2-*a*:2′,3′-*d*]imidazole and Its Benzo and Aza Analogues via an Orthogonal Tandem Intermolecular Pd-Catalyzed and Intramolecular Cu-Catalyzed Amination. A round-bottom flask of 50 mL was charged with $Pd_2(dba)_3$ (0.030 mmol, 0.028 g, 2.0 mol %), XANTPHOS (0.066 mmol, 0.038 g, 4.4 mol %), and DME (5 mL). The obtained mixture was flushed with N_2 for 10 min under magnetic stirring. Meanwhile, a pressure tube of 80 mL was charged with CuI (0.15 mmol, 0.028 g, 10 mol %), 2,3-dibromopyridine (**1**) (1.5 mmol, 0.355 g), amidine (**2**) (1.8 mmol), and cesium carbonate (6.0 mmol, 1.955 g). To this mixture was added the preformed Pd catalyst under a N_2 flow. The flask of 50 mL was subsequently rinsed with 2 × 5 mL of DME. Then, the resulting mixture was flushed with N_2 for 5 min, sealed, and heated (internal temperature: 140 °C, oil bath temperature: 160 °C) under vigorous magnetic stirring for 24 h. After cooling the reaction mixture to room temperature, 20 mL of dichloromethane was added and the suspension was filtered over a glass filter. The filter was rinsed (a) with dichloromethane (130 mL) for components **4a**−**4c** or (b) with 7 N NH_3 in MeOH (200 mL) and dichloromethane (130 mL) for components **4d** and **4e**. The filtrate was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (97:3) as the eluent.

Dipyrido[1,2-*a*:2′,3′-*d*]imidazole (4a). The general procedure was followed using 2-aminopyridine (**2a**) (1.80 mmol, 0.169 g) as amidine: yield 0.205 g (80%); white solid; mp 197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.82 (1H, dd, J = 4.7, 1.4 Hz, H_2), 8.54 (1H, d, J = 6.7 Hz, H_6), 8.27 (1H, dd, J = 8.1, 1.4 Hz, H_4), 7.83 (1H, d, J = 9.3 Hz, H_9), 7.54 (1H, dd, J = 9.3, 6.7 Hz, H_8), 7.30 (1H, dd, J = 8.1, 4.7 Hz, H_3), 6.97 (1H, t, J = 6.7 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) 155.9, 149.6, 148.9, 131.2, 126.1, 121.4, 119.2, 118.5, 116.3, 111.8; HRMS (ESI) for $C_{10}H_7N_3$ $[M + H]^+$ calcd 170.0718, found 170.0711.

Pyrido[2′,3′:4,5]imidazo[1,2-*a*]quinoline (4b). The general procedure was followed using 2-aminoquinoline (**2b**) (1.80 mmol, 0.259 g) as amidine: yield 0.290 g (88%); white solid; mp 207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.82 (1H, d, J = 4.6 Hz, H_2), 8.66 (1H, d, J = 8.2 Hz, H_4), 8.46 (1H, d, J = 8.6 Hz, H_6), 7.89 (1H, dd, J = 7.7, 1.4 Hz, H_9), 7.80 (1H, td, J = 8.6, 1.4 Hz, H_7), 7.79 (1H, d, J = 9.4 Hz, H_{10}), 7.73 (1H, d, J = 9.4 Hz, H_{11}), 7.54 (1H, t, J = 7.7 Hz, H_8), 7.42 (1H, dd, J = 8.2, 4.6 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 156.7, 149.8, 147.2, 135.6, 132.5, 130.3, 130.2, 124.9, 123.5, 121.9, 118.0, 117.4, 115.2; HRMS (ESI) for $C_{14}H_{10}N_3$ $[M + H]^+$ calcd 220.0875, found 220.0873.

Pyrido[3′,2′:4,5]imidazo[2,3-*a*]isoquinoline (4c). The general procedure was followed using 1-aminoisoquinoline (**2c**) (1.80 mmol, 0.259 g) as amidine. The reaction mixture was heated for 30 h: yield 0.284 g (86%); white solid; mp >250 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$) 8.93 (1H, m, H_8 or H_{11}), 8.78 (1H, dd, J = 4.7, 1.4 Hz, H_2), 8.15 (1H, d, J = 7.2 Hz, H_6), 8.13 (1H, dd, J = 8.1, 1.4 Hz, H_4), 7.78−7.71 (3H, m, H_{11} or H_8, H_9 and H_{10}), 7.33 (1H, dd, J = 8.1, 4.7 Hz, H_3), 7.15 (1H, d, J = 7.2 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) 156.3, 148.9, 147.5, 131.8, 130.9, 128.7, 127.3, 126.1, 123.5, 122.7, 121.35, 118.0, 116.9, 112.4; HRMS (ESI) for $C_{14}H_{10}N_3$ $[M + H]^+$ calcd 220.0875, found 220.0869.

Pyrido[2′,3′:4,5]imidazo[1,2-*a*]pyrazine (4d). The general procedure was followed using aminopyrazine (**2d**) (1.80 mmol, 0.171 g) as amidine: yield 0.109 g (44%); white solid; mp 229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 9.43 (1H, d, J = 1.5 Hz, H_9), 9.00 (1H, dd, J = 4.5, 1.5 Hz, H_7), 8.38 (1H, dd, J = 4.6, 1.5 Hz, H_2), 8.34 (1H, dd, J = 8.2, 1.5 Hz, H_4), 8.09 (1H, d, J = 4.5 Hz, H_6), 7.47 (1H, dd, J = 8.2, 4.6 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 155.4, 150.9, 146.2, 142.7, 128.2, 120.3, 119.9, 118.1, 118.1; HRMS (ESI) for $C_{10}H_6N_4$ $[M + H]^+$ calcd 171.0671, found 171.0663.

Pyrido[2′,3′:4,5]imidazo[1,2-*b*]pyridazine (4e). The general procedure was followed using 4.0 mol % $Pd_2(dba)_3$, 8.8 mol % XANTPHOS, and 3-aminopyridazine (**2e**) (1.80 mmol, 0.171 g) as amidine. The reaction mixture was heated for 30 h: yield 0.193 g (76%); white solid; mp 159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.90 (1H, dd, J = 4.6, 1.4 Hz, H_2), 8.49 (1H, dd, J = 8.1, 1.6 Hz, H_4), 8.47 (1H, dd, J = 4,5, 1.6 Hz, H_7), 8.17 (1H, dd, J = 9.4, 1.6 Hz, H_9), 7.44 (1H, dd, J = 8.1, 4.6 Hz, H_3), 7.36 (1H, dd, J = 9.4, 4.5 Hz, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) 154.6, 149.8, 144.1, 142.1, 126.8, 123.1, 122.5, 120.4, 118.2; HRMS (ESI) for $C_{10}H_6N_4$ $[M + H]^+$ calcd 171.0671, found 171.0664.

General Procedure for the Synthesis of Dipyrido[1,2-*a*:2′,3′-*d*]imidazole and Its Benzo and Aza Analogues via an Auto-Tandem Inter- and Intramolecular Pd-Catalyzed Amination. A round-bottom flask of 50 mL was charged with $Pd_2(dba)_3$ (0.030 mmol, 0.028 g, 2.0 mol %), XANTPHOS (9,9-dimethyl-4,5-bis-(diphenylphosphanyl)-9*H*-xanthene) (0.066 mmol, 0.038 g, 4.4 mol %), and DME (5 mL). The obtained mixture was flushed with N_2 for 10 min under magnetic stirring. Meanwhile, a pressure tube of 80 mL was charged with 2,3-dibromopyridine (**1**) (1.5 mmol, 0.355 g), amidine (**2**) (1.8 mmol), and cesium carbonate (6.0 mmol, 1.955 g). To this mixture was added the preformed Pd catalyst under a N_2 flow. The flask of 50 mL was subsequently rinsed with 2 × 5 mL of DME. Then, the resulting mixture was flushed with N_2 for 5 min, sealed, and heated (internal temperature: 140 °C, oil bath temperature: 160 °C) under vigorous magnetic stirring for 24 h. After cooling the reaction mixture to room temperature, 20 mL of dichloromethane was added and the suspension was filtered over a glass filter. The filter was rinsed (a) with dichloromethane (130 mL) for components **4a**−**4c** or (b) with 7 N NH_3 in MeOH (200 mL) and dichloromethane (130 mL) for components **4d** and **4e**. The filtrate was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (97:3) as the eluent.

(22) Only the dipyrido[1,2-*a*:2′,3′-*d*]imidazole skeleton and some substituted analogues are known: (a) Chezal, J. M.; Moreau, E.; Chavignon, O.; Gaumet, V.; Métin, J.; Blache, Y.; Diez, A.; Fradera, X.; Luque, J.; Teulade, J. C. *Tetrahedron* **2002**, *58*, 295. (b) Baklanov, M. V.; Frolov, A. N. *Zh. Org. Khim.* **1991**, *27*, 638.

(23) Trace amounts (<5%) of dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo and aza analogues were also isolated. These regioisomers are presumably formed via tandem C-3 intermolecular and C-2 intramolecular metal-catalyzed amination.

Dipyrido[1,2-*a*:2′,3′-*d*]imidazole (4a). The general procedure was followed using 2-aminopyridine (**2a**) (1.80 mmol, 0.169 g) as amidine: yield 0.010 g (4%).

Pyrido[2′,3′:4,5]imidazo[1,2-*a*]quinoline (4b). The general procedure was followed using 2-aminoquinoline (**2b**) (1.80 mmol, 0.259 g) as amidine: yield 0.306 g (93%).

Pyrido[3′,2′:4,5]imidazo[2,3-*a*]isoquinoline (4c). The general procedure was followed using 1-aminoisoquinoline (**2c**) (1.80 mmol, 0.259 g) as amidine: yield 0.252 g (76%).

Pyrido[2′,3′:4,5]imidazo[1,2-*a*]pyrazine (4d). The general procedure was followed using aminopyrazine (**2d**) (1.80 mmol, 0.171 g) as amidine: yield 0.013 g (5%).

Pyrido[2′,3′:4,5]imidazo[1,2-*b*]pyridazine (4e). The general procedure was followed using 3-aminopyridazine (**2e**) (1.80 mmol, 0.171 g) as amidine: yield 0.250 g (97%).

General Procedure for the Synthesis of *N*-(3-Bromopyridin-2-yl)azaheteroarylamines. A round-bottom flask of 50 mL was charged with $Pd_2(dba)_3$ (0.030 mmol, 0.028 g, 2.0 mol %), XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphanyl)-9*H*-xanthene) (0.066 mmol, 0.038 g, 4.4 mol %), and DME (5 mL). The obtained mixture was flushed with N_2 for 10 min under magnetic stirring. Meanwhile, a round-bottom flask of 100 mL was charged with 2,3-dibromopyridine (**1**) (1.5 mmol, 0.355 g), amidine (**2**) (1.8 mmol), and cesium carbonate (6.0 mmol, 1.955 g). To this mixture was added the preformed Pd catalyst under a N_2 flow. The flask of 50 mL was subsequently rinsed with 2 × 5 mL of DME. Then, the resulting mixture was flushed with N_2 for 5 min and heated at reflux (oil bath temperature: 95 °C) (N_2 atmosphere) under vigorous magnetic stirring for 7 h. After cooling the reaction mixture to room temperature, 20 mL of dichloromethane was added and the suspension was filtered over a glass filter. The filter was rinsed with dichloromethane (130 mL), and the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (99:1) as the eluent.

3-Bromo-*N*-pyridin-2-ylpyridin-2-amine (3a). The general procedure was followed using 2-aminopyridine (**2a**) (1.80 mmol, 0.169 g) as amidine: yield 0.343 g (91%); white solid; mp 44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.44 (1H, dd, J = 8.5, 1.0 Hz), 8.27 (1H, d, J = 4.9 Hz), 8.22 (1H, dd, J = 4.8, 1.7 Hz), 7.89 (1H, s), 7.78 (1H, dd, J = 7.7, 1.7 Hz), 7.68 (1H, dd, J = 8.5, 7.2 Hz), 6.95 (1H, ddd, J = 7.2, 4.9, 1.0 Hz), 6.73 (1H, dd, J = 7.7, 4.8); ^{13}C NMR (100 MHz, $CDCl_3$) 153.2, 151.0, 148.1, 147.0, 140.7, 138.0, 118.0, 117.9, 112.5, 107.2; IR ($CHCl_3$, cm^{-1}) 3398.5; HRMS (ESI) for $C_{10}H_9N_3Br$ $[M + H]^+$ calcd 249.9980, found 249.9989.

***N*-(3-Bromopyridin-2-yl)quinolin-2-amine (3b).** The general procedure was followed using 2-aminoquinoline (**2b**) (1.80 mmol, 0.259 g) as amidine: yield 0.447 g (99%); white solid; mp 124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.60 (1H, d, J = 9.0 Hz), 8.25 (1H, d, J = 4.7 Hz), 8.13 (1H, d, J = 9.0 Hz), 8.06 (1H, s, NH), 7.84 (1H, d, J = 7.9 Hz), 7.82 (1H, dd, J = 8.0, 1.5 Hz), 7.75 (1H, dd, J = 8.2, 1.2 Hz), 7.64 (1H, ddd, J = 8.2, 7.0, 1.5 Hz), 7.39 (1H, ddd, J = 8.0, 7.0, 1.2 Hz), 6.77 (1H, dd, J = 7.9, 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 152.6, 151.0, 147.4, 146.4, 141.0, 137.9, 129.9, 127.7, 127.3, 125.8, 124.4, 117.4, 114.0; IR ($CHCl_3$, cm^{-1}) 3392.9; HRMS (ESI) for $C_{14}H_{11}N_3Br$ $[M + H]^+$ calcd 300.0136, found 300.0124.

***N*-(3-Bromopyridin-2-yl)isoquinolin-1-amine (3c).** The general procedure was followed using 4.0 mol % $Pd_2(dba)_3$, 8.8 mol % XANTPHOS, and 1-aminoisoquinoline (**2c**) (1.80 mmol, 0.259 g) as amidine: yield 0.445 g (91%); yellow solid; mp 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 14.79 (1H, s), 8.96 (1H, br d, J = 8.1 Hz), 8.21 (1H, dd, J = 4.9, 1.5 Hz), 7.93 (1H, d, J = 7.5 Hz), 7.64 (1H, br t, J = 7.7 Hz), 7.55 (1H, ddd, J = 8.1, 7.1, 1.3 Hz), 7.51 (1H, br d, J = 7.7 Hz), 7.22 (1H, d, J = 6.6 Hz), 6.72 (1H, dd, J = 7.5, 4.9 Hz), 6.63 (1H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 159.2, 152.8, 144.2, 141.0, 136.4, 131.9, 127.5, 126.5, 126.2, 118.4, 116.7, 108.4; IR ($CHCl_3$, cm^{-1}) 3386.9; HRMS (ESI) for $C_{14}H_{11}N_3Br$ $[M + H]^+$ calcd 300.0136, found 300.0139.

***N*-(3-Bromopyridin-2-yl)pyrazin-2-amine (3d).** The general procedure was followed using 4.0 mol % $Pd_2(dba)_3$, 8.8 mol % XANTPHOS, and aminopyrazine (**2d**) (1.80 mmol, 0.171 g) as amidine: yield 0.346 g (92%); white solid; mp 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 9.79 (1H, d, J = 1.3 Hz), 8.27 (1H, dd, J = 4.8, 1.5), 8.23 (2H, m), 7.82 (1H, dd, J = 7.9, 1.5 Hz), 7.76 (1H, s), 6.80 (1H, dd, J = 7.9, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 150.2, 149.8, 146.6, 142.2, 141.0, 138.2, 136.2, 117.8, 107.0; IR ($CDCl_3$, cm^{-1}) 3392.4; HRMS (ESI) for $C_9H_8N_4Br$ $[M + H]^+$ calcd 250.9932, found 250.9944.

***N*-(3-Bromopyridin-2-yl)pyridazin-3-amine (3e).** The general procedure was followed using 3-aminopyridazine (**2e**) (1.80 mmol, 0.171 g) as amidine: yield 0.304 g (81%); white solid; mp 88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.84 (1H, dd, J = 4.6, 1.4 Hz), 8.72 (1H, dd, J = 9.1, 1.4 Hz), 8.31 (1H, s), 8.22 (1H, dd, J = 4.8, 1.6 Hz), 7.85 (1H, dd, J = 7.8, 1.6 Hz), 7.43 (1H, dd, J = 9.1, 4.6 Hz), 6.80 (1H, dd, J = 7.8, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 156.6, 150.6, 147.1, 146.3, 141.2, 127.7, 117.9, 117.4, 107.5; IR ($CDCl_3$, cm^{-1}) 3384.6; HRMS (ESI) for $C_9H_8N_4Br$ $[M + H]^+$ calcd 250.9932, found 250.9921.

Attempts to Synthesize 3b, 3c, and 3e via an Intramolecular Amination without the Addition of a Pd or Cu Catalyst. A 10 mL microwave vial was charged with *N*-(3-bromopyridin-2-yl)-azaheteroarylamine (**3**) (0.5 mmol), cesium carbonate (2.0 mmol, 0.652 g), and DME (5 mL). Then, the resulting mixture was flushed with N_2 for 5 min, sealed, and heated (oil bath temperature: 160 °C) under vigorous magnetic stirring for 24 h. After cooling the reaction mixture to room temperature, 20 mL of dichloromethane was added and the suspension was filtered over a glass filter. The filter was rinsed (a) with dichloromethane (50 mL) for components **4b** and **4c** or (b) with 7 N NH_3 in MeOH (100 mL) and dichloromethane (50 mL) for component **4e**. The filtrate was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (99:1) as the eluent to isolate **3**, followed by dichloromethane/methanol (97:3) for **4**.

Pyrido[2′,3′:4,5]imidazo[1,2-*a*]quinoline (4b). The general procedure was followed using *N*-(3-bromopyridin-2-yl)quinolin-2-amine (**3b**) (0.5 mmol, 0.150 g) as amidine: yield 0.059 g (53%).

Pyrido[3′,2′:4,5]imidazo[2,3-*a*]isoquinoline (4c). The general procedure was followed using *N*-(3-bromopyridin-2-yl)isoquinolin-1-amine (**3c**) (0.5 mmol, 0.150 g) as amidine: yield 0.102 g (92%).

Pyrido[2′,3′:4,5]imidazo[1,2-*b*]pyridazine (4e). The general procedure was followed using *N*-(3-bromopyridin-2-yl)pyridazin-3-amine (**3e**) (0.5 mmol, 0.125 g) as amidine: yield 0.014 g (16%).

Acknowledgment. We would like to thank the Fund for Scientific Research−Flanders (Belgium) (project 1.5.088.04 and PhD scholarship ("Aspirant") for C.M.), the European Union, and the University of Antwerp (NOI BOF UA 2005) for financial support.

Supporting Information Available: More detailed information and ^{1}H NMR spectra of all compounds. Tables A−C. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052091U